

Understand and underestimating exercise as medicine: Why and how fast does the heart benefit from exercise?

Dick H.J. Thijssen, Laween Uthman, Yasina Begum Somani, and Niels van Royen

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The following individual(s) involved in review of this submission have agreed to reveal their identity: Shane A Phillips (Referee #1); Huub - Maas (Referee #2)

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Reviewing Editor: Simon Gandevia

Transaction Report:

(Note: With the exception of the correction of typographical or spelling errors that could be a source of ambiguity, letters and reports are not edited. Depending on transfer agreements, referee reports obtained elsewhere may or may not be included in this compilation. Referee reports are anonymous unless the Referee chooses to sign their reports.)

Dear Dr Thijssen,

Re: JP-SR-2021-282000 "Understand and underestimating exercise as medicine: Why and how fast does the heart benefit from exercise?" by Dick H.J. Thijssen, Laween Uthman, Yasina Begum Somani, and Niels van Royen

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I look forward to receiving your revised submission.

If you have any queries please reply to this email and staff will be happy to assist.

Yours sincerely,

Ian D. Forsythe
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EDITOR COMMENTS

Reviewing Editor:

This is a timely review of a neat evolving concept. The submission is well written and easy to follow. The reviewers identify areas where there could be definite improvement to increase the real information content and ultimately the impact of the review. The figures are clear and helpful. However, I strongly recommend that the species be mentioned for particular research findings.

REFEREE COMMENTS

Referee #1:

This is an interesting review paper which suggests that there is a window of opportunity for exercise to improve and protect against cardiovascular risk and ischemia reperfusion injury. The overarching idea is that short term exercise protection attenuates the cardiac and vascular injury risk. The idea is novel and is supported by the literature reviewed in the paper. The primary concern is that the literature reviewed on intensity of SEP and CV protection lacks details on the specific exercise prescription. This makes it difficult to discern what the intensity level or duration of protections based on intensity might be. In addition, there is minimal discussion and review of mode of SEP. A table may help to guide the reader. Much of the discussion of the mechanisms of signaling is speculative and could be toned down. Lastly, the title does not seem clear. I would make it specific to short term exercise induced protection of CV function/health.

Referee #2:

The manuscript presents a review on a relatively new concept, i.e. Short-term Exercise induced Protection, which appears to result in cardiovascular protection. In three sections, the authors describe the evidence of SEP, the modulators of the protection and the potential underlying mechanism. The text is well structured and the literature is reviewed in a concise manner. Below my comments.

- The authors describe results from pre-clinical studies in which a variety of animal models are exploited. Reporting of the species, strain and sex is however not consistently done. At the minimum the species needs to be mentioned when describing these studies. The authors make only one remark about the results being transferrable across different species, but it is not clear if this is the case for all animal models described. Some critical notes regarding the potential for translation to humans seems warranted.
- The second key point is not a conclusion of this review. This could be replaced by the sentence in the abstract "SEP activates multiple pathways to confer...".
- Instead of ending the abstract with stating that future directions are discussed, it is more informative if the actual directions are described.
- In the section on mechanisms, several abbreviations are used but they are not consistently defined. Also a brief description of their general function like done for PKC would be helpful for the non-expert reader.

END OF COMMENTS

Confidential Review

18-Jun-2021

Dear Professor Kim E. Barrett, editor-in-chief of *the Journal of Physiology*,

We would like to submit the revision of the original manuscript entitled: entitled: "*Understanding and underestimating exercise as medicine: Why and how fast does the heart benefit from exercise?*", now entitled "*Short term exercise-induced protection of cardiovascular function and health: Why and how fast does the heart benefit from exercise?*" as a symposium review accompanying the Second International Motor Impairment Conference.

The main feedback presented by the reviewers was related to reporting of relevant information from the studies presented in this manuscript. This includes the species, strain, age and exercise prescription. In the revised manuscript, we have included two tables that describe each of these factors, together with the ischemia-reperfusion injury protocol, the outcome of the study and potential mechanisms related to the observed protection. In addition, changes in the main text have been made accordingly, which better define the species type used in the studies that were discussed. We endeavor that these textual changes and the addition of the two tables will elaborate more on the current evidence for single-/short-term exercise-induced preconditioning (SEP) against cardiac ischemia/reperfusion injury.

Second, the manuscript has touched upon some of the mechanisms of SEP that were previously investigated. Since this area of preconditioning by exercise has been largely overlooked, as opposed to ischemic preconditioning strategies, most of the data exploring the mechanisms are retrieved from animal-based work. This makes it difficult to pinpoint intracellular pathways and effector signaling molecules related to the effectiveness of SEP. We have aimed to connect and describe some of the explored mechanisms in the original manuscript, but to ensure appropriate extrapolation and translation of these animal-based studies, we have refined the conclusions made on the mechanisms of SEP in this revised submission. In addition, we have included several suggestions for future studies that would benefit the translation of SEP.

This manuscript has not previously been published and is not under consideration elsewhere. I hereby confirm that all authors have approved this manuscript.

On behalf of all contributing authors,

Yours sincerely,

Dick Thijssen, (corresponding author)
Laween Uthman,
Yasina Somani
Niels van Royen

EDITOR COMMENTS

Reviewing Editor:

This is a timely review of a neat evolving concept. The submission is well written and easy to follow. The reviewers identify areas where there could be definite improvement to increase the real information content and ultimately the impact of the review. The figures are clear and helpful. However, I strongly recommend that the species be mentioned for particular research findings.

We thank the reviewing editor for the thorough review of our work. We have now included information regarding the species used in the mentioned studies. In addition, we have highlighted the species for each study in **table 1**, followed by the methods and outcomes and mechanisms explored by each study.

REFeree COMMENTS

Referee #1:

This is an interesting review paper which suggests that there is a window of opportunity for exercise to improve and protect against cardiovascular risk and ischemia reperfusion injury. The overarching idea is that short term exercise protection attenuates the cardiac and vascular injury risk. The idea is novel and is supported by the literature reviewed in the paper. The primary concern is that the literature reviewed on intensity of SEP and CV protection lacks details on the specific exercise prescription. This makes it difficult to discern what the intensity level or duration of protections based on intensity might be. In addition, there is minimal discussion and review of mode of SEP. A table may help to guide the reader. Much of the discussion of the mechanisms of signaling is speculative and could be toned down. Lastly, the title does not seem clear. I would make it specific to short term exercise induced protection of CV function/health.

We thank the reviewer for the remarks and critical revision of our work. We agree with the lack of data regarding the exercise protocol implemented in the studies reviewed. Since there is minimal evidence on the mode of SEP in relation to ischemia/reperfusion injury, it is difficult to review and discuss that factor. However, we have now included two tables for the evidence from animal and human studies, respectively, where intensity, duration and the number of repetitions have been elaborated (**table 1 and 2**). In addition, we have made textual changes by adding a paragraph to discuss the duration of SEP (**pages 10-11**), the mechanisms, and have toned down speculative conclusions (throughout **pages 11-15**). We have also changed the title as suggested by the reviewer to: "*Short term exercise-induced protection of cardiovascular function and health: Why and how fast does the heart benefit from exercise?*".

Referee #2:

The manuscript presents a review on a relatively new concept, i.e. Short-term Exercise induced Protection, which appears to result in cardiovascular protection. In three sections, the authors describe the evidence of SEP, the modulators of the protection and the potential underlying mechanism. The text is well structured and the literature is reviewed in a concise manner. Below my comments.

We value the reviewer's critical revision of our manuscript. Please find our responses below each comment.

- The authors describe results from pre-clinical studies in which a variety of animal models are exploited. Reporting of the species, strain and sex is however not consistently done. At the minimum the species needs to be mentioned when describing these studies. The authors make only one remark about the results being transferrable across different species, but it is not clear if this is the case for all animal models described. Some critical notes regarding the potential for translation to humans seems warranted.

We agree with the reviewer that the information regarding the animal population used in the studies was inadequately reported in our previous manuscript. Therefore, we have included two tables summarizing the most important aspects for each human and animal study that was included and discussed in our manuscript (**table 1 and 2**). These tables include information related to species, model and sex, but also exercise type, the outcome of the study in relation to cardioprotective effects, and the potential mechanisms that were examined in relation to SEP.

In only one study, the transfer of circulating effector signaling following SEP was evaluated in isolated perfused rabbit hearts [1]. To clarify that the transfer of SEP has so far only been demonstrated between two different species (rabbit and human), we have made textual arrangements stating that this transfer of SEP is transferable across two species (**page 11**).

Finally, we have highlighted the factors and potential perspectives for translation of animal-derived evidence of SEP by proposing the use of large animal models. Specifically, mechanistic explorations and translation to human populations seems feasible, whilst cross-species models (human-to-animal) are available to investigate feasibility of exercise in human subjects, while investigating the effectiveness of interventions against cardiac I/R-injury outcome in animal tissue (**page 16**). This information may be informative for those readers interested in the field and perform research in this area.

- The second key point is not a conclusion of this review. This could be replaced by the sentence in the abstract "SEP activates multiple pathways to confer..."

The second key point has now been adjusted to: *"SEP activates multiple pathways to confer cardiac protection, which develops remotely at the site of the activated muscle by release of circulating molecules, which transfer towards activation of intramyocardial signaling that promotes cell survival during episodes of IR injury."* (page 2).

We agree with the reviewer, as this statement should better fit as a conclusion derived from this manuscript.

- Instead of ending the abstract with stating that future directions are discussed, it is more informative if the actual directions are described.

We agree with this reviewer and we have changed the ending of the abstract to: *"Finally, we discuss potential future directions for designing adequate human and animal studies that will*

support developing effective SEP strategies for the (multi-)diseased and aged individual.”
(page 3).

- In the section on mechanisms, several abbreviations are used but they are not consistently defined. Also a brief description of their general function like done for PKC would be helpful for the non-expert reader.

We thank the reviewer for this observation. In the revised manuscript, the abbreviations are explained, and for each of the intracellular molecules an additional statement is added explaining the function (**pages 14-15**).

Reference

1. Michelsen, M.M., et al., *Exercise-induced cardioprotection is mediated by a bloodborne, transferable factor*. Basic Res Cardiol, 2012. **107**(3): p. 260.

Dear Professor Thijssen,

Re: JP-SR-2021-282000R1 "Understand and underestimating exercise as medicine: Why and how fast does the heart benefit from exercise?" by Dick H.J. Thijssen

Laween Uthman

Yasina Begum Somani

Niels van Royen

I am pleased to tell you that your Symposium Review article has been accepted for publication in The Journal of Physiology, subject to any modifications to the text that may be required by the Journal Office to conform to House rules.

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Yours sincerely,

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Comments:

Reviewing Editor:

The manuscript has been thoughtfully revised and hopefully will be a useful resource for researchers in the future.

REFeree COMMENTS:

Referee #1:

This is a nice review of the impact of exercise on vascular function. I have no further comments.

Referee #2:

All comments were addressed adequately.

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1st Confidential Review

01-Nov-2021
